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Commentary on the WHO classification of tumors of lymphoid tissues (2008): aggressive B-cell lymphomas

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Abstract In the novel WHO classification 2008, the classification of aggressive B-cell lymphoma has been revised for several categories with the aim to define “clean” entities. Within large B-cell lymphoma, a few distinct clinico-pathological entities have been recognized with more clinically defined entities than pathologically defined ones. The majority of known morphological variations were not considered to merit more than classification as a variant of DLBCL, not otherwise specified. Specifically, a biological subgrouping of DLBCL on the basis of molecular (activated B-cell versus germinal center B-cell) or immunophenotypic

(CD5+) features was felt to be too immature to include at this stage. The role of EBV in aggressive B-cell lymphoma has been explored in more depth with the recognition of several novel and re-defined clinico-pathological entities. Also, in these diseases, clinical definitions play a very dominant role in the WHO classification 2008.

Keywords Diffuse large B-cell lymphoma · Clinico-pathological entity · EBV · Immunodeficiency · Classification · WHO

Introduction

Aggressive B-cell lymphomas encompass several categories within diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), and various morphologically, biologically, and clinically distinct diseases of large B-cells. Over the past years, research data on the relationships, overlapping features, and essential differences between various categories of aggressive B-cell lymphomas have served as the basis of discussions to separate new categories or to lump together others in the WHO classification 2008 [1]. EBV-associated B-cell lymphoma and overlapping features between DLBCL and BL on one hand and cHL on the other hand have been a focus of attention. In this paper, issues in DLBCL and EBV-associated B-cell lymphoma will be discussed. The issue of lymphomas with overlapping features between DLBCL and BL and DLBCL and cHL will be discussed separately.

Diffuse large B-cell lymphoma

Proliferations of large B-cells can be classified in different ways. Morphology-based classification has been the classi-

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cal approach for pathologists. However, more modern approaches may focus on biological categories, clinical categories, or even categories that reflect responsiveness to therapies. For the WHO classification 2008, clinico-pathological categories have been separated, and an attempt has been made to define biological categories. As compared to the WHO classification 2001, the prior “waste basket” of neoplastic proliferations of large B-cells has been more extensively subdivided into biologically homogeneous entities with the introduction of five new entities and the promotion of three from variants status of DLBCL to independent distinct entities in recognition of their biological uniqueness (Table 1).

The large group of proliferations of large B-cells is lumped together as diffuse large B-cell lymphoma, not otherwise specified in parallel to the nomenclature in peripheral T-cell lymphoma. In situations where there is insufficient evidence to justify delineation as a separate

entity, the term “variants”, “subgroups”, and “subtypes” are used. The variants of DLBCL contain morphologically remarkable features, but do not represent biologically distinct groups. It is noteworthy that some believe that the so-called immunoblastic lymphoma category from previous classifications merits recognition as a distinct entity since it includes the activated B-cell (ABC) type DLBCL and is characterized by a worse prognosis. The only real importance to define such features is to consciously highlight the morphological spectrum of the disease and thereby avoid some pitfalls in daily practice (e.g., T-cell-rich B-cell lymphoma mistaken for T-cell lymphoma or the anaplastic variant of DLBCL mistaken for metastatic carcinoma).

T-cell/histiocyte-rich large B-cell lymphoma (THRBCL) holds a special position by its morphological overlap and possible biological relation to nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). The authors of the

Table 1 Classification of aggressive B-cell lymphomas

WHO classification 2001

Diffuse large B-cell lymphoma

Morphological variants

Centroblastic
Immunoblastic
Anaplastic
T-cell/histiocyte rich

Rare variants/immunophenotypic subtypes

Plasmablastic lymphoma
DLBCL with expression of full length ALK

Mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

Lymphomatoid granulomatosis

Primary effusion lymphoma

Burkitt lymphoma

Endemic BL
Sporadic BL
Immunodeficiency-associated BL
BL with plasmacytoid differentiation
Atypical BL/Burkitt like

WHO classification 2008

Diffuse large B-cell lymphoma, not otherwise specified

Common morphological variants

Centroblastic
Immunoblastic
Anaplastic

Rare morphological variants

Molecular subgroups

Germinal center B-cell like
Activated B-cell like

Immunohistochemical subgroups

CD5-positive DLBCL
Germinal center B-cell like
Non-germinal center B-cell like

Diffuse large B-cell lymphoma, subtypes

T-cell/histiocyte-rich large B-cell lymphoma

Primary DLBCL of CNS

Primary cutaneous DLBCL, leg-type

EBV positive DLBCL of the elderly (provisional entity)

Primary mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

DLBCL associated with chronic inflammation

Lymphomatoid granulomatosis

ALK-positive DLBCL

Plasmablastic lymphoma

Large B-cell lymphoma arising in HHV8 associated with multicentric Castleman disease

Primary effusion lymphoma

Burkitt lymphoma

Endemic BL
Sporadic BL
Immunodeficiency-associated BL

Borderline cases

B-cell lymphoma, unclassifiable, with features between DLBCL and Burkitt lymphoma

B-cell lymphoma, unclassifiable, with features between DLBCL and classical Hodgkin lymphoma

Data in bold are entities discussed in separate chapters; data in italics are subgroups discussed within larger chapters; data in blue are newly introduced entities and subgroups

DLBCL chapter consider diffuse areas of large B-cells in a background of small T-cells and histiocytes in a lymph node that is otherwise involved in NPLHL as “THRBCL-like areas” not indicative of transformation to aggressive disease NPLHL as a variant of DLBCL, while the authors of the NPLHL chapter leave this issue open and thus it remains controversial. It is agreed upon, however, that the detection of only a single nodule with features of NPLHL suffices to exclude a diagnosis of primary THRBCL, and in this sense, the definition is much sharper than in the WHO classification 2001.

Molecular and immunophenotypic subgrouping in DLBCL, NOS

It has been debated if it would be timely to introduce gene-expression based biological subgrouping of DLBCL in the WHO classification 2008. In 2000, DLBCL with gene-expression profiles of germinal center B-cells and activated B-cell-like were first described. Subsequently, it was found that both groups carry characteristic genetic aberrations and yet may be morphologically indistinguishable to a large extent. Since gene-expression profiling is not generally available for diagnostic purposes in daily practice, “translations” to immunohistochemical algorithms have been defined, including the so-called Hans-algorithm [2]. However, the immunophenotypic subdivision only correlates to the gene-expression subgrouping in around 80% of the cases; thus, the reproducibility of the immunophenotypic classification is suboptimal, and the prognostic impact is conflicting. Similar considerations regarding a lack of reproducibility and biological and prognostic impact can apply for the CD5+ DLBCL, considered a immunohistochemical subgroup in the WHO classification 2008 [3–5]. Therefore, immunohistochemical and molecular subgroups of DLBCL, NOS are only considered as variants with a similar level of relative (un) importance as morphologic variants, but not advocated as separate entities. Indeed, there is no justification to use this information for treatment stratification and for use in routine clinical practice. This situation may be quite different in experimental treatment programs, and it can be expected that introduction of some form of “biomarker”-based treatment stratification will find its way into practice in the coming few years. Up to that time, however, it is debatable whether to include this type of information in routine pathology reports without extensive comments on its interpretation for clinicians.

Clinico-pathological subtypes of large B-cell lymphomas

Both in the listing of “DLBCL, subtypes” and the “other lymphomas of large B-cells”, clinico-pathological subtypes

that may be mostly defined by clinical features are found: primary DLBCL of CNS, primary cutaneous DLBCL, leg-type, EBV-positive DLBCL of the elderly, and intravascular large B-cell lymphoma. Of these, intravascular large B-cell lymphoma was also described in the WHO classification 2001. The others are newly introduced entities.

Primary DLBCL of CNS has been introduced to describe primary intracerebral and intraocular DLBCL, excluding lymphomas of the dura, intravascular large B-cell lymphoma, secondary CNS localizations and lymphomas in immunodeficient patients. Apart from the typical clinical situation, these lymphomas are mostly distinctive by biological features related to the immune-privileged character of the primary site. These include microenvironment modulation by IL-4, loss of HLA class I and II protein expression, and immunoglobulin structure (extreme Ig hypermutation in concert with retention of an open reading frame) [6]. Identical features are found in lymphomas at other immune-privileged sites such as testis. Perhaps future classifications may consider combining primary DLBCL in the testis together with primary DLBCL of the CNS as a new entity of DLBCL involving immunoprivileged sites.

Herpes-virus (EBV/HHV8)-related large B-cell proliferations

Several large B-cell proliferations related to EBV infection and/or immunodeficiency status have been recognized in the 2008 WHO classification as separate entities or introduced as new ones (Table 1).

The common feature of these processes is the association of an immunodeficiency status with an EBV or HHV-8 related B-cell neoplasm (Table 2). The three newly introduced entities (EBV-positive diffuse large B-cell lymphoma of the elderly, DLBCL associated with chronic inflammation and large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease) depict mainly the clinical setting in which the lymphoma originated. The recognition of factors such as age and chronic inflammation (not only pyothorax-associated) as causes of immunodeficiency in EBV-associated DLBCL in the absence of any other primary or secondary immune disease prompted the segregation of these into two clinico-pathological categories. Although molecular studies have shown that DLBCL associated with chronic inflammation and nodal diffuse large B-cell lymphoma have significant different gene-expression profiles, EBV-positive diffuse large B-cell lymphoma of the elderly and DLBCL associated with chronic inflammation have no single morphological or phenotypical feature that distinguish them from DLBCL not otherwise specified (NOS). Therefore, the clinico-pathological correlation is the gold standard in the proper

Table 2 Features of Herpes-virus-related lymphoid neoplasms

	EBV-positive diffuse large B-cell lymphoma of the elderly	DLBCL associated with chronic inflammation	Lymphomatous granulomatosis	Plasmablastic lymphoma	Primary effusion lymphoma	Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
EBV positivity	100%	100%	60–75%	100%	90%	0%
HHV8 positivity	–	–	–	–	100%	100%
Characteristic morphological features	–	–	Inflammatory background, angiotropic, and angiodestructive	Immunoblastic/plasmablastic	Immunoblastic/plasmablastic	Plasmablastic, perifollicular arrangement
Characteristic immunophenotype	–	–	–	CD20–, PAX5–, CD138+, MUM1+	CD20–, CD79a–, Ig–, CD138+, EMA+, CD30+	CD20+, Ig+
Characteristic clinical features	Age >50	Long-standing chronic inflammatory process (>10 years) primary extranodal (pleural cavity)	Primary extranodal (pulmonary, brain, kidney, skin)	Oral cavity, other extranodal sites	Pleural, pericardial, peritoneal cavity	Multicentric Castleman disease
Primary immunodeficiency	–	–	+ (Wiskott–Aldrich syndrome)	–	–	–
HIV	–	–	+	+	+	+
Organ transplant	–	–	+	+	+	–
Other iatrogenic immunodeficiencies	–	–	+	+	+	–
Elderly	+	–	–	+	+	+
					(in HHV8 endemic areas)	(in HHV8 endemic areas)

diagnosis of these entities. Most cases show a post-germinal center phenotype, and a subset of them have an immunoblast/plasmablast morphology and phenotype, concordantly with the plasma cell differentiation induced by EBV. Similar to post-transplant lymphoproliferative disorders, tumor cells express LMP-1 and EBNA-2 hence a latency pattern III, known as the growth program. Cells expressing the EBV growth program are restricted to the naive B-cell subset in healthy individuals. It might be that in the absence of immune surveillance, EBV-infected germinal center or memory B-cells can switch to latency III and undergo clonal expansion. The expression of the full spectrum of latent EBV genes indicates an important role for the virus in driving proliferation of the infected B-cells [7, 8].

Multicentric Castleman disease is associated with HHV8 infection, and this situation may evolve into a specific type of large B-cell lymphoma, particularly in HIV+ patients. The B-cell lymphoma occurring in this clinical setting was initially defined as a plasmablastic lymphoma because the postulated cell of origin morphologically resembles a plasmablast. However, the tumor cells are often CD20 positive and represent a naive IgM secreting cell without somatic hypermutations [9–11]. These cases must be

distinguished from the oral type plasmablastic lymphoma that is EBV positive and HHV8 negative.

Plasmablastic lymphoma of the oral type was regarded in the former WHO classification as a subtype of DLBCL associated with HIV infection. Later descriptions have reported cases of plasmablastic lymphoma outside of this clinical setting and even in patients without any known cause of immunodeficiency [12]. The WHO 2008 classification has broadened the definition of the previous classification to other localizations apart from the oral mucosa and also to other immunodeficiency states other than HIV infection. Plasmablastic lymphoma presents mostly in extranodal sites and in the majority of cases is associated with EBV infection. Tumor cells have immunoblastic morphology with a mature plasma cell phenotype. Clonal IgH rearrangement is demonstrable, and the IgH genes may show evidence of somatic hypermutation or be in an unmutated configuration [13]. The monotonous morphological appearance of the majority of these tumors reflects the lack of a T-cell host response. In these cases, LMP-1 is rarely expressed, and the most frequent latency pattern is type-I, in which EBNA-1 does not serve as a target for CD8 cytotoxic T lymphocytes [7]. The lack of co-stimulatory surface molecules helps the

tumor cells to escape from immunological recognition, but also leaves as an open question the role of EBV in the pathogenesis of these lymphomas.

All the entities described above are characterized by a very aggressive behavior and short survival regardless of International Prognostic Index and stage at diagnosis. The immunosuppressed state in the most part of patients contributes to the poor clinical course. Additionally, downregulation of HLA class I expression [14] and activation of the IL-6 [15] receptor signaling pathway have been described in some cases as mechanisms of escape from host cytotoxic T lymphocytes. This is not unlike the mechanisms by which DLBCL of immunoprivileged sites maintain immune-escape.

Previous attempts to segregate different hematolymphoid entities usually started with the observation of morphological features characteristic of a disease and then a later description of a cytogenetic or molecular alteration that now are part of the definition of the entity. In DLBCL, the morphologic, phenotypic, and clinical heterogeneity has led the efforts to segregate different subgroups. In the last WHO classification, several entities with overlapping morphological features have been separated based on clinical features; molecular and cytogenetic studies are required to better understand the biological basis of these entities.

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